Air Force Health Study

An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides

SAIC Team

Russell H. Roegner, Ph.D.
William D. Grubbs, Ph.D.
Michael B. Lustik, M.S.
Amy S. Brockman, M.S.
Scott C. Henderson, M.S.
David E. Williams, M.D., SCRF

Air Force Team

Col William H. Wolfe, M.D., M.P.H.
Joel E. Michalek, Ph.D.
Col Judson C. Miner, D.V.M., M.P.H.

Project Manager: R.H. Roegner
Statistical Task Manager: W.D. Grubbs
SAIC Quality Review Chair: W.F. Thomas
SAIC Editors: Cynthia A. Marut
Elisabeth M. Smeda

Program Manager: R.W. Ogershok

SCIENCE APPLICATIONS INTERNATIONAL CORPORATION
8400 Westpark Drive
McLean, VA 22102

EPIDEMIOLOGY RESEARCH DIVISION
ARMSTRONG LABORATORY
HUMAN SYSTEMS DIVISION (AFSC)
Brooks Air Force Base, TX 78235

In conjunction with

SCRIPPS CLINIC & RESEARCH FOUNDATION, LA JOLLA, CA

NATIONAL OPINION RESEARCH CENTER, CHICAGO, IL

March 1991

Volume VII

SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

Contract Number: F41689-86-D-0010
SAIC Project Number: 1-813-X4-195/254/437/011/942/943

AIR FORCE HEALTH STUDY

An Epidemiologic Investigation of
Health Effects in Air Force Personnel
Following Exposure to Herbicides

March 1991

VOLUME VII

SERUM DIOXIN ANALYSIS OF 1987 EXAMINATION RESULTS

EPIDEMIOLOGY RESEARCH DIVISION
ARMSTRONG LABORATORY
HUMAN SYSTEMS DIVISION (AFSC)
Brooks Air Force Base, Texas 78235

TABLE OF CONTENTS

VOLUME VII

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS - REPORT

CHAPTER 17

PULMONARY ASSESSMENT

INTRODUCTION

Background

Research into the pulmonary toxicity of dioxin in laboratory animals has been limited to in vitro investigation at the cellular and subcellular level in contrast to other organ systems. Much of this work has focused on the physicochemical properties of the cytosolic aryl hydroxylase (Ah) receptor and the cytochrome P-450 enzyme system in mice (1), rats (2, 3), and rabbits (4-8).

Isolation of the Ah receptor in human lung tissue has heightened interest in the relevance of these animal studies to the potential for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced pneumotoxicity in man. In one study (9), cytosol preparations were examined from human lung tissue specimens obtained at surgery. Only 10 of 53 specimens had detectable Ah receptors at concentrations far less (10% to 30%) than those found in lung cytosols from laboratory animals. The authors raised the possibility that the Ah receptor may be genetically determined and speculated on the role it may play in individual susceptibility to lung cancer.

Lung disease has been included infrequently as a clinical endpoint in epidemiologic studies of humans exposed to phenoxy herbicides. In one report (10), standard pulmonary function tests were included in clinical examinations of 367 employees 30 years after an industrial explosion associated with high-level exposure to 2,4,5,-T and, by contamination, TCDD. Among current cigarette smokers, lung function assessed by static and flow-dependent indices appeared significantly compromised in the exposed cohort relative to the unexposed. In contrast, test parameters were essentially equal in nonsmokers and former smokers in both the exposed and unexposed group.

Apart from local irritative symptoms occurring in industrial accidents, there is no clinical evidence that the human lung is a target organ for TCDD toxicity. A single case of hypersensitivity pneumonitis was described in a Vietnam veteran occupationally exposed to herbicides (11) though there was no scientific basis to support a causal relationship to TCDD. The respiratory failure that has been reported in rare cases of extreme phenoxyherbicide intoxication appears to be related to central nervous system depression rather than primary pneumotoxicity (12, 13).

Finally, several large-scale epidemiologic studies of military veterans have included chest x rays and pulmonary function tests in the examination protocols (14, 15). To date, there is no evidence for any increased incidence of pulmonary disease related to herbicide exposure or to military service in Vietnam.

More detailed summaries of the pertinent scientific literature for the pulmonary assessment can be found in the report of the previous analyses of the 1987 examination data (14).

Summary of Previous Analyses of the 1987 Examination Data

The pulmonary assessment was based on five self-reported respiratory illnesses, seven clinical observations, and eight laboratory measurements. No evidence of a herbicide effect was detected in the assessment of the reported respiratory illnesses. The health of the two groups was reasonably comparable based on the clinical and laboratory variables, although the Ranch Hands had a significantly higher percentage of thorax and lung abnormalities on examination than the Comparisons, based on the unadjusted analysis, and a marginally higher percentage after adjustment for covariates. No significant group differences were detected in the adjusted analyses without significant interactions involving group. Exploration of the group-by-covariate interactions did not reveal a consistent pattern indicating a herbicide effect. The adverse effects of smoking on pulmonary status were evident in all analyses.

Parameters of the Pulmonary Assessment

Dependent Variables

Questionnaire, physical examination, and laboratory data were used in the pulmonary assessment.

Questionnaire Data

In the self-administered family and personal history section, each study participant was asked whether he had ever experienced the following conditions: asthma, bronchitis, pleurisy, pneumonia, and tuberculosis. This self-reported information was combined with information from the 1987 questionnaire and the Baseline and 1985 examinations and subsequently verified by medical record review. These five variables were analyzed as a measure of the pulmonary health status of each participant.

Participants with pre-Southeast Asia (SEA) tour occurrences of asthma, bronchitis, pleurisy, pneumonia, or tuberculosis were excluded from the respective analyses.

Physical Examination Data

Part of the pulmonary assessment was based on the results of the physical examination of the thorax and lungs. The following six variables from the physical examinations were analyzed in the pulmonary assessment: asymmetrical expansion, hyperresonance, dullness, wheezes, rales, and thorax and lung abnormalities (a composite variable including all of the previous conditions, some of which are mutually exclusive [hyperresonance and dullness]). These variables were coded as yes/no.

No participants were excluded for medical reasons from the analysis of these variables.

Laboratory Examination Data

The assessment of the laboratory examination data included the analysis of pulmonary abnormalities detected on a routine chest x ray. This variable was coded as normal/abnormal.

The assessment also included the analysis of pulmonary physiologic data collected during the physical examination employing standard spirometric techniques. Numerous indices were derived including (1) forced vital capacity (FVC), a measurement of the amount of air in liters expelled from maximum inspiration to full expiration; (2) forced expiratory volume (FEV), in liters, an index derived from the FVC that quantifies the amount of air expelled at 1 second (FEV_1); and (3) forced expiratory flow maximum (FEFmax), an index of peak instantaneous flow in liters per second during a forced expiration. The values used for these variables were the percentages of predicted values rather than the actual volume or flow rate. The calculations of these percentages included an adjustment for age and height, as prescribed by the American Thoracic Society. The Scripps Clinic and Research Foundation laboratory has the same predictive values regardless of race. For these indices, lower values indicate greater compromise in the lung function. In addition, the ratio of observed FEV_1 to observed FVC was calculated as an index reflective of obstructive airway disease. These variables were analyzed as continuous variables. For the ratio of observed FEV_1 to observed FVC, the natural logarithm of 1 minus the ratio transformation was used. Loss of vital capacity and obstructive abnormality were classified as none, mild, moderate, or severe and were analyzed as part of the pulmonary assessment. Results judged to be between none and mild were classified as mild for all analyses. A similar methodology was used for results between mild and moderate (i.e., classified as moderate), and between moderate and severe (i.e., classified as severe). Due to the low frequencies in the moderate and severe categories, these two categories were combined in the analysis.

As a guide for determining abnormal pulmonary function, readings below the 95th percentile are considered abnormal for the FVC and FEV_1. For men above 36 years of age, the corresponding percent of predicted is 74 percent for the FVC and 73 percent for the FEV_1. An FVC or FEV_1 below 40 percent of predicted is considered severely impaired, as recommended by the American Thoracic Society. The division between mild, moderate, and severe impairment is arbitrarily defined by dividing the interval between severe impairment and the lower limit of normal into two equal bands. That is, the cutpoint between mild and moderate impairment is at 57 percent of the predicted value. Although the other spirometric indices (FEFmax and FEV_1/FVC) and the appearance of the flow volume curve are useful to the physician interpreting the test, there are insufficient data to support arbitrary lower limits of normal or cutpoints to classify impairment as mild, moderate, or severe.

No participants were excluded for medical reasons from the analysis of these variables.

Covariates

The effects of age, race, current cigarette smoking, and lifetime cigarette smoking history were used in adjusted statistical analyses evaluating the pulmonary dependent variables. Current cigarette smoking and lifetime cigarette smoking history were based on self-reported questionnaire data.

Age, current cigarette smoking, and lifetime cigarette smoking history were used in the continuous form for modeling purposes in all general linear models and logistic regression analyses; these variables were discretized for use in log-linear analyses. These covariates were also discretized for presentation purposes (e.g., interaction summaries).

Relation to Baseline, 1985, and 1987 Studies

In general, the same variables that were analyzed in the serum dioxin analysis were analyzed at Baseline, although a slightly different classification of reported pulmonary disease was used in the Baseline analyses. In the 1985 examination, the pulmonary physiology data were not collected. The questionnaire variables analyzed in the serum dioxin analysis were updated from the previous self-reported information to reflect verified results. The physical examination data analyzed in the serum dioxin analysis were also analyzed for the 1985 examination and the previous analysis of the 1987 examination.

In the longitudinal analysis, group differences in the changes between the 1987 examination and Baseline in the ratio of observed FEV_1 to observed FVC were analyzed.

Statistical Methods

Table 17-1 summarizes the statistical analyses performed for the pulmonary assessment. The first part of this table lists the dependent variables analyzed, the source of the data, the form of the data (discrete or continuous), cutpoints (if applicable), the candidate covariates, and the statistical methods. The basic statistical analysis methods used are described in Chapter 4, Statistical Methods. The second part of this table provides a further description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in footnotes. The number of participants with missing dependent variable data and those excluded due to pre-SEA conditions are provided in Table 17-2.

Since no asymmetric expiration abnormalities were found, analyses were not conducted. The analyses of tuberculosis and dullness were adjusted only for main effects.

Appendix P-1 contains graphic displays of pulmonary dependent variables versus initial dioxin for the minimal and maximal Ranch Hand cohorts, and pulmonary dependent variables versus current dioxin for Ranch Hands and Comparisons. Graphics for dioxin-by-covariate interactions determined by various statistical models are presented in Appendix P-2. A guide to assist in interpreting the graphics is found in Chapter 4.

Three statistical models were used to examine the association between a pulmonary dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the pulmonary dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (14). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion.

TABLE 17-1.

Statistical Analysis for the Pulmonary Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Asthma	Q/PE-V	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Bronchitis	Q/PE-V	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Pleurisy	Q/PE-V	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Pneumonia	Q/PE-V	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Tuberculosis	Q/PE-V	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Thorax and Lung Abnormalities	PE	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Asymmetric Expansion	PE	D	Yes No	--	--
Hyperresonance	PE	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Dullness	PE	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Wheezes	PE	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Rales	PE	D	Yes No	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
X-Ray Interpretation	LAB	D	Abnormal Normal	AGE,RACE, CSMOK,PACKYR	U:LR A:LR
Forced Vital Capacity (FVC) (percent of predicted)	LAB	C	--	AGE,RACE, CSMOK,PACKYR	U:GLM A:GLM

TABLE 17-1. (Continued)

Statistical Analysis for the Pulmonary Assessment

Dependent Variables

Variable (Units)	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Forced Expiratory Volume in 1 Second (FEV_1) (percent of predicted)	LAB	C	--	AGE,RACE, CSMOK,PACKYR	U:GLM A:GLM
Forced Expiratory Flow Maximum (FEFmax) (percent of predicted)	LAB	C	--	AGE,RACE, CSMOK,PACKYR	U:GLM A:GLM
Ratio of Observed FEV_1 to Observed FVC	LAB	C	--	AGE,RACE, CSMOK,PACKYR	U:GLM A:GLM L:GLM
Loss of Vital Capacity	LAB	D	Moderate/ Severe Mild None	AGE,RACE, CSMOK,PACKYR	U:LL A:LL
Obstructive Abnormality	LAB	D	Moderate/ Severe Mild None	AGE,RACE, CSMOK,PACKYR	U:LL A:LL

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black

TABLE 17-1. (Continued)

Statistical Analysis for the Pulmonary Assessment

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Current Cigarette Smoking (CSMOK) (cigarettes/day)	Q-SR	D/C	0-Never 0-Former >0-20 >20
Lifetime Cigarette Smoking History (PACKYR) (pack-years)	Q-SR	D/C	0 >0-10 >10

Abbreviations

Data Source:
LAB--1987 SCRF laboratory results
MIL--Air Force military records
PE--1987 SCRF physical examination
Q/PE-V--Questionnaire and physical examination (verified)
Q-SR--Questionnaire (self-reported)

Data Form:
C--Continuous analysis only
D--Discrete analysis only
D/C--Appropriate form for analysis (either discrete or continuous)

Statistical Analyses:
U--Unadjusted analyses
A--Adjusted analyses
L--Longitudinal analyses

Statistical Methods:
GLM--General linear models analysis
LL--Log-linear models analysis
LR--Logistic regression analysis

TABLE 17-2.

Number of Participants Excluded and With Missing Data for the Pulmonary Assessment

Variable	Variable Use	Assumption (Ranch Hands Only)		Categorized Current Dioxin	
		Minimal	Maximal	Ranch Hand	Comparison
Pre-SEA Asthma	EXC	6	10	9	8
Pre-SEA Bronchitis	EXC	17	26	21	24
Pre-SEA Pleurisy	EXC	3	5	7	6
Pre-SEA Pneumonia	EXC	25	37	38	34
Pre-SEA Tuberculosis	EXC	4	4	6	4
X-Ray Interpretation	DEP	2	2	3	2
FVC	DEP	0	0	1	0
FEV_1	DEP	0	0	1	0
FEFmax	DEP	0	0	1	0
Ratio of Observed FEV_1 to Observed FVC	DEP	0	0	1	0
Loss of Vital Capacity	DEP	0	0	1	0
Obstructive Abnormality	DEP	0	0	1	0

DEP--Dependent variable (missing data).
EXC--Exclusion.

RESULTS

Exposure Analysis

Questionnaire Variables

Asthma

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, there was no significant association between asthma and initial dioxin for both the minimal and the maximal cohorts (Table 17-3 [a] and [b]: p=0.678 and p=0.473).

In the adjusted minimal analysis, a significant interaction between initial dioxin and current cigarette smoking was exhibited (Table 17-3 [c]: p<0.001). To examine this interaction, current cigarette smoking was divided into four strata: never smoked, formerly smoked, smoked no more than 20 cigarettes per day, and smoked over 20 cigarettes per day. The relative risks were not significant in the strata containing Ranch Hands with no current cigarette use (Appendix Table P-1: never smoked: p=0.756; formerly smoked: p=0.618). In the other strata, there were marginally significant risks that were less than 1 (>0-20 cigarettes/day: Adj. RR=0.06, p=0.062; >20 cigarettes/day: Adj. RR: 0.00, p=0.052). However, for those who smoked no more than 20 cigarettes per day, there were only two participants with asthma in the low initial dioxin category and one in the medium initial dioxin category. For those who smoked more than 20 cigarettes per day, there were only two participants with asthma, and both in the low initial dioxin category.

There was also a significant interaction between initial dioxin and current cigarette smoking in the adjusted maximal analysis (Table 17-3 [d]: p=0.024). The only current cigarette smoking stratum in which the relative risk was significant was for those Ranch Hands who smoked more than 20 cigarettes per day (Appendix Table P-1: Adj. RR=0.29, p=0.034). The percentages of asthma occurrences in this stratum were 17.9, 1.6, and 0.0 percent for the low, medium, and high initial dioxin levels. When this interaction was removed from the model, the association between asthma and initial dioxin remained nonsignificant (Table 17-3 [d]: p=0.290).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both assumptions, the current dioxin-by-time since tour interaction was nonsignificant in the unadjusted analyses of asthma (Table 17-3 [e] and [f]: minimal, p=0.358; maximal, p=0.176). In the adjusted models, the current dioxin-by-time interaction remained nonsignificant (Table 17-3 [g] and [h]: minimal, p=0.324; maximal, p=0.141).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast in the unadjusted analysis showed no significant association between asthma occurrences and the current dioxin categories (Table 17-3 [i]: p=0.228). However, when contrasting the unknown category with the background category, the risk of asthma was significantly greater than 1 (Est. RR=2.34, 95% C.I.: [1.04,5.25], p=0.040).

TABLE 17-3.

Analysis of Asthma

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=515)	Low	128	4.7	0.91 (0.59,1.41)	0.678
	Medium	258	1.9		
	High	129	3.9		
b) Maximal (n=732)	Low	183	4.9	0.89 (0.66,1.22)	0.473
	Medium	366	3.0		
	High	183	2.7		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=515)	****	****	INIT*CSMOK (p<0.001) AGE (p=0.003)
d) Maximal (n=732)	0.85 (0.62,1.16)**	0.290**	INIT*CSMOK (p=0.024) AGE (p=0.042) RACE (p=0.084)

[a]Relative risk for a twofold increase in dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

****Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); adjusted relative risk, confidence interval, and p-value not presented.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
INIT: Log_2 (initial dioxin).

TABLE 17-3. (Continued)

Analysis of Asthma

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.358[b]
(n=515)	≤18.6	5.7 (70)	2.3 (128)	5.6 (54)	1.17 (0.66,2.06)	0.590[c]
	>18.6	5.2 (58)	0.8 (130)	2.7 (75)	0.76 (0.36,1.62)	0.474[c]
f) Maximal						0.176[b]
(n=732)	≤18.6	3.9 (104)	4.2 (189)	3.6 (83)	1.12 (0.75,1.67)	0.571[c]
	>18.6	3.9 (78)	2.8 (176)	2.0 (102)	0.71 (0.42,1.23)	0.223[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.324[b]	AGE (p=0.028)
(n=515)	≤18.6	1.05 (0.57,1.95)	0.866[c]	RACE (p=0.131)
	>18.6	0.65 (0.28,1.48)	0.303[c]	
h) Maximal			0.141[b]	AGE (p=0.052)
(n=732)	≤18.6	1.05 (0.69,1.59)	0.811[c]	RACE (p=0.066)
	>18.6	0.64 (0.36,1.12)	0.116[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-3. (Continued)

Analysis of Asthma

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	778	1.5	All Categories		0.228
Unknown	340	3.5	Unknown vs. Background	2.34 (1.04,5.25)	0.040
Low	194	2.1	Low vs. Background	1.34 (0.43,4.21)	0.612
High	185	2.7	High vs. Background	1.77 (0.62,5.10)	0.288
Total	1,497				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	778	All Categories		0.213	AGE (p=0.144)
Unknown	340	Unknown vs. Background	2.42 (1.07,5.47)	0.033	
Low	194	Low vs. Background	1.33 (0.43,4.18)	0.621	
High	185	High vs. Background	1.57 (0.54,4.58)	0.406	
Total	1,497				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

After adjusting the model for age, the overall contrast remained nonsignificant (Table 17-3 [j]: p=0.213). The risk under the unknown versus background contrast remained significant (Adj. RR=2.42, 95% C.I.: [1.07,5.47], p=0.033).

Bronchitis

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The association between bronchitis and initial dioxin was not significant under both assumptions in the unadjusted analysis (Table 17-4 [a] and [b]: minimal, p=0.269; maximal, p=0.128). After the models were adjusted for covariates, the association remained nonsignificant under the minimal assumption (Table 17-4 [c]: p=0.277). However, under the maximal assumption, the risk of bronchitis was marginally less than 1 when age and lifetime cigarette smoking history were retained in the model (Table 17-4 [d]: Adj. RR=0.86, p=0.062). The percentages of bronchitis occurrences in the low, medium, and high initial dioxin categories were 17.1, 13.0, and 13.3 percent.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant under both the minimal and the maximal assumptions in the unadjusted analysis of bronchitis (Table 17-4 [e] and [f]: p=0.281 and p=0.161, respectively). The only significant relative risk of bronchitis in the unadjusted analyses was under the maximal assumption when time was less than or equal to 18.6 years (Table 17-4 [f]: Est. RR=0.76, p=0.044). The percentages of bronchitis occurrences in this stratum were 19.2, 13.6, and 8.6 percent for the low, medium, and high current dioxin levels.

In the adjusted minimal analysis there was a significant interaction among current dioxin, time, and race (Table 17-4 [g]: p=0.015). In the stratum containing Blacks, for time less than or equal to 18.6 years, there was only one participant with bronchitis in the low current dioxin category, one in the medium category, and none in the high category (Appendix Table P-1). For time greater than 18.6 years, there were no Blacks with bronchitis in the low and medium categories and two in the high category.

In the stratum containing non-Blacks, the current dioxin-by-time interaction was nonsignificant (Appendix Table P-1: p=0.415), as was the negative association between asthma and current dioxin within each time strata (p=0.106 for time $\leq$18.6; p=0.344 for time >18.6). After the current dioxin-by-time-by-race interaction was removed from the model, the current dioxin-by-time interaction remained nonsignificant (Table 17-4 [g]: p=0.257). However, the risk of bronchitis, within the time less than or equal 18.6 years stratum, became marginally significant when race and the current cigarette smoking-by-lifetime cigarette smoking history interaction were retained in the model (Adj. RR=0.69, p=0.099). In the low, medium, and high current dioxin categories within this stratum, 15.2, 12.6, and 7.7 percent of the participants had bronchitis.

In the adjusted maximal analysis there was also a significant interaction among current dioxin, time, and race (Table 17-4 [h]: p<0.001). The Black stratum contained two participants with asthma in the low current dioxin category, two in the medium category, and none in the high category when time was less than or equal to 18.6 years, and only two partici-

TABLE 17-4.

Analysis of Bronchitis

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=504)	Low	122	16.4	0.88 (0.70,1.11)	0.269
	Medium	254	13.0		
	High	128	10.9		
b) Maximal (n=716)	Low	175	17.1	0.88 (0.75,1.04)	0.128
	Medium	361	13.0		
	High	180	13.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=504)	0.88 (0.70,1.11)	0.277	CSMOK*PACKYR (p=0.017)
d) Maximal (n=716)	0.86 (0.73,1.01)	0.062	AGE (p=0.055) PACKYR (p=0.043)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-4. (Continued)

Analysis of Bronchitis

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.281[b]
(n=504)	≤18.6	15.2 (66)	12.6 (127)	7.7 (52)	0.71 (0.47,1.08)	0.106[c]
	>18.6	16.1 (56)	14.2 (127)	13.2 (76)	0.93 (0.70,1.24)	0.623[c]
f) Maximal						0.161[b]
(n=716)	≤18.6	19.2 (99)	13.6 (184)	8.6 (81)	0.76 (0.58,0.99)	0.044[c]
	>18.6	15.6 (77)	13.9 (173)	13.7 (102)	0.97 (0.78,1.19)	0.750[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.257**[b]	CURR*TIME*RACE (p=0.015)
(n=504)	≤18.6	0.69 (0.45,1.07)**	0.099**[c]	CSMOK*PACKYR (p=0.013)
	>18.6	0.93 (0.70,1.24)**	0.627**[c]	
h) Maximal			****	CURR*TIME*RACE (p<0.001)
(n=716)	≤18.6	****	****	AGE (p=0.054)
	>18.6	****	****	RACE*PACKYR (p=0.015)

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.
****Log_2 (current dioxin)-by-time-by-covariate interaction ($p\leq0.01$); adjusted relative risk, confidence interval, and p-value not presented.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
CURR: Log_2 (current dioxin).
TIME: Time since tour.

TABLE 17-4. (Continued)

Analysis of Bronchitis

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	762	13.1	All Categories		0.437
Unknown	333	16.2	Unknown vs. Background	1.28 (0.89,1.84)	0.176
Low	191	13.6	Low vs. Background	1.04 (0.66,1.66)	0.858
High	183	11.5	High vs. Background	0.86 (0.52,1.42)	0.549
Total	1,469				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	762	All Categories		0.533**	DXCAT*AGE (p=0.043)
Unknown	333	Unknown vs. Background	1.25 (0.87,1.80)**	0.227**	PACKYR (p=0.009)
Low	191	Low vs. Background	1.02 (0.64,1.63)**	0.927**	RACE*CSMOK (p=0.042)
High	183	High vs. Background	0.87 (0.52,1.44)**	0.579**	
Total	1,469				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
DXCAT: Categorized current dioxin.

pants with bronchitis in the high category when time was greater than 18.6 years (Appendix Table P-1). In the non-Black stratum, the current dioxin-by-time interaction was nonsignificant (Appendix Table P-1: p=0.265). However, when time was less than or equal to 18.6 years, the risk of bronchitis was significantly less than 1 (Adj. RR=0.73, p=0.030). The percentages of bronchitis occurrences within the low, medium, and high current dioxin categories were 17.9, 13.4, and 8.9 percent.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis, the overall contrast exhibited no significant association between bronchitis and the current dioxin categories (Table 17-4 [i]: p=0.437).

In the adjusted analysis, there was a significant interaction between categorized current dioxin and age (Table 17-4 [j]: p=0.043). To explore this interaction, age was divided into two strata: participants born during or after 1942 and those born before 1942. In the younger stratum, the overall contrast was not significant (Appendix Table P-1: p=0.196). However, there was a marginally significant risk of bronchitis when the unknown category was contrasted with the background category (Adj. RR=1.80, 95% C.I.: [0.98,3.28], p=0.057). In the stratum containing the older participants, the overall contrast was also nonsignificant (p=0.130). However, when contrasting the high category against the background category, the risk of bronchitis was significantly less than 1 (Adj. RR=0.35, 95% C.I.: [0.12,1.00], p=0.050). After the categorized current dioxin-by-age interaction was removed, the overall contrast remained nonsignificant (Table 17-4 [j]: p=0.533).

Pleurisy

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and the maximal assumptions, the association between pleurisy and initial dioxin was not significant in the unadjusted analysis (Table 17-5 [a] and [b]: p=0.190 and p=0.253, respectively). However, in the adjusted model, there was a marginally significant risk of pleurisy under the minimal assumption (Table 17-5 [c]: Adj. RR=1.41, p=0.090). The percentages of pleurisy occurrences in the low, medium, and high initial dioxin categories were 1.5, 3.1, and 4.6 percent. The interaction between age and race was retained in this model. Under the maximal assumption, the relative risk remained nonsignificant (Table 17-5 [d]: p=0.158).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of pleurisy, the current dioxin-by-time since tour interaction was not significant under both assumptions (Table 17-5 [e] and [f]: minimal, p=0.944; maximal, p=0.452).

In the adjusted analysis, under the minimal assumption, there was a significant interaction among current dioxin, time, and race (Table 17-5 [g]: p<0.001). Within the Black stratum there were only two participants with pleurisy: one in the time less than or equal to 18.6 years stratum under the low current dioxin category, the other in the time greater than 18.6 years stratum under the high current dioxin category (Appendix Table P-1). In the non-Black stratum the current dioxin-by-time interaction was not significant (p=0.463).

TABLE 17-5.

Analysis of Pleurisy

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=518)	Low	130	1.5	1.29 (0.89,1.87)	0.190
	Medium	258	3.1		
	High	130	4.6		
b) Maximal (n=737)	Low	184	2.2	1.19 (0.89,1.58)	0.253
	Medium	369	2.4		
	High	184	4.9		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=518)	1.41 (0.96,2.07)	0.090	AGE*RACE (p=0.022)
d) Maximal (n=737)	1.25 (0.93,1.68)	0.158	AGE*RACE (p=0.025)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-5. (Continued)

Analysis of Pleurisy

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.944[b]
(n=518)	≤18.6	1.4 (72)	0.8 (128)	5.6 (54)	1.22 (0.56,2.66)	0.612[c]
	>18.6	3.5 (58)	3.9 (130)	5.3 (76)	1.18 (0.76,1.84)	0.455[c]
f) Maximal						0.452[b]
(n=737)	≤18.6	2.8 (106)	1.6 (191)	3.6 (83)	0.95 (0.55,1.65)	0.864[c]
	>18.6	2.6 (78)	2.8 (176)	5.8 (103)	1.22 (0.86,1.74)	0.273[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
g) Minimal			****	CURR*TIME*RACE (p<0.001)
(n=518)	≤18.6	****	****	
	>18.6	****	****	
h) Maximal			****	CURR*TIME*RACE (p=0.007)
(n=737)	≤18.6	****	****	AGE*RACE (p=0.008)
	>18.6	****	****	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

****Log_2 (current dioxin)-by-time-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value not presented.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-5. (Continued)

Analysis of Pleurisy

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	780	3.9	All Categories		0.263
Unknown	341	3.2	Unknown vs. Background	0.83 (0.41,1.68)	0.611
Low	194	1.6	Low vs. Background	0.39 (0.12,1.30)	0.126
High	186	4.8	High vs. Background	1.27 (0.59,2.73)	0.537
Total	1,501				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	780	All Categories		0.183	AGE*PACKYR (p=0.018)
Unknown	341	Unknown vs. Background	0.80 (0.39,1.61)	0.527	
Low	194	Low vs. Background	0.39 (0.12,1.30)	0.126	
High	186	High vs. Background	1.47 (0.67,3.20)	0.332	
Total	1,501				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Under the maximal assumption, there was also a significant interaction among current dioxin, time, and race (Table 17-5 [h]: p=0.007). The Black stratum contained only two participants with pleurisy, one in each time strata (Appendix Table P-1). For time less than or equal to 18.6 years, the only participant with pleurisy was in the medium current dioxin category. For time greater than 18.6 years, the only participant with pleurisy was in the high current dioxin category. In the non-Black stratum, the current dioxin-by-time interaction was not significant (Appendix Table P-1: p=0.668).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast of the four current dioxin categories in the unadjusted analysis exhibited no significant association between pleurisy and current dioxin (Table 17-5 [i]: p=0.263). In the adjusted analysis, the overall contrast was also nonsignificant (Table 17-5 [j]: p=0.183).

Pneumonia

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

No significant association between pneumonia and initial dioxin was exhibited in both the minimal and the maximal cohorts in the unadjusted analysis (Table 17-6 [a] and [b]: p=0.693 and p=0.545, respectively). After both models were adjusted for significant covariates, the associations remained nonsignificant (Table 17-6 [c] and [d]: minimal, p=0.791; maximal, p=0.489).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of pneumonia, the current dioxin-by-time since tour interaction was not significant under both assumptions (Table 17-6 [e] and [f]: minimal, p=0.931; maximal, p=0.828). This interaction remained nonsignificant even after the models were adjusted for significant covariates (Table 17-6 [g] and [h]: minimal, p=0.947; maximal, p=0.773).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

According to the overall contrast of the four current dioxin categories, the association between the current dioxin categories and pneumonia occurrences was not significant in both the unadjusted and the adjusted models (Table 17-6 [i] and [j]: unadjusted, p=0.740; adjusted, p=0.782).

Tuberculosis

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The association between tuberculosis and initial dioxin was not significant in the unadjusted analyses of both the minimal and the maximal cohorts (Table 17-7 [a] and [b]: p=0.359 and p=0.386).

After the model was adjusted for covariates, the association remained nonsignificant under both assumptions (Table 17-7 [c] and [d]: minimal, p=0.458; maximal, p=0.419).

TABLE 17-6.

Analysis of Pneumonia

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=496)	Low	121	8.3	0.94 (0.71,1.25)	0.693
	Medium	248	6.9		
	High	127	8.7		
b) Maximal (n=705)	Low	175	9.1	0.94 (0.77,1.15)	0.545
	Medium	349	7.2		
	High	181	8.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=496)	0.96 (0.72,1.29)	0.791	PACKYR (p=0.045) AGE*RACE (p=0.049)
d) Maximal (n=705)	0.93 (0.75,1.15)	0.489	PACKYR (p=0.016) AGE*RACE (p=0.025)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-6. (Continued)

Analysis of Pneumonia

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=496)						0.931[b]
	≤18.6	11.8 (68)	6.6 (122)	11.5 (52)	0.98 (0.64,1.48)	0.907[c]
	>18.6	5.5 (55)	7.2 (125)	5.4 (74)	0.95 (0.63,1.43)	0.809[c]
f) Maximal (n=705)						0.828[b]
	≤18.6	11.7 (103)	8.9 (180)	8.6 (81)	0.94 (0.70,1.25)	0.653[c]
	>18.6	5.6 (72)	6.6 (168)	5.9 (101)	0.98 (0.72,1.34)	0.903[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=496)			0.947[b]	PACKYR (p=0.049)
	≤18.6	1.00 (0.66,1.53)	0.993[c]	
	>18.6	0.98 (0.65,1.48)	0.932[c]	
h) Maximal (n=705)			0.773[b]	PACKYR (p=0.013)
	≤18.6	0.91 (0.68,1.24)	0.565[c]	AGE*RACE (p=0.035)
	>18.6	0.97 (0.71,1.34)	0.872[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-6. (Continued)

Analysis of Pneumonia

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	752	9.3	All Categories		0.740
Unknown	324	8.3	Unknown vs. Background	0.89 (0.56,1.41)	0.609
Low	184	7.6	Low vs. Background	0.80 (0.44,1.46)	0.470
High	182	7.1	High vs. Background	0.75 (0.41,1.39)	0.358
Total	1,442				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	752	All Categories		0.782	PACKYR (p=0.008) RACE*CSMOK (p=0.047)
Unknown	324	Unknown vs. Background	0.86 (0.54,1.38)	0.542	
Low	184	Low vs. Background	0.81 (0.44,1.47)	0.486	
High	182	High vs. Background	0.78 (0.42,1.45)	0.433	
Total	1,442				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 17-7.

Analysis of Tuberculosis

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=517)	Low	129	4.7	0.80 (0.49,1.32)	0.359
	Medium	259	2.3		
	High	129	1.6		
b) Maximal (n=738)	Low	185	3.2	0.86 (0.61,1.22)	0.386
	Medium	369	3.3		
	High	184	1.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=517)	0.83 (0.51,1.37)	0.458	PACKYR (p=0.071)
d) Maximal (n=738)	0.86 (0.60,1.24)	0.419	RACE (p=0.054) PACKYR (p=0.004)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-7. (Continued)

Analysis of Tuberculosis

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.614[b]
(n=517)	≤18.6	6.9 (72)	0.8 (126)	1.9 (53)	0.65 (0.27,1.56)	0.339[c]
	>18.6	3.5 (58)	3.0 (132)	1.3 (76)	0.86 (0.45,1.64)	0.650[c]
f) Maximal						0.834[b]
(n=738)	≤18.6	2.8 (106)	3.7 (189)	1.2 (82)	0.81 (0.47,1.39)	0.435[c]
	>18.6	3.8 (79)	2.8 (179)	1.9 (103)	0.87 (0.54,1.40)	0.567[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.601[b]	PACKYR (p=0.073)
(n=517)	≤18.6	0.68 (0.28,1.65)	0.396[c]	
	>18.6	0.91 (0.48,1.72)	0.769[c]	
h) Maximal			0.821[b]	RACE (p=0.054)
(n=738)	≤18.6	0.81 (0.46,1.44)	0.477[c]	PACKYR (p=0.004)
	>18.6	0.89 (0.53,1.47)	0.640[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-7. (Continued)

Analysis of Tuberculosis

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	782	3.2	All Categories		0.486
Unknown	344	3.5	Unknown vs. Background	1.09 (0.54,2.20)	0.801
Low	194	2.1	Low vs. Background	0.64 (0.22,1.85)	0.408
High	185	1.6	High vs. Background	0.50 (0.15,1.67)	0.260
Total	1,505				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Categories		0.486	--
Unknown	344	Unknown vs. Background	1.09 (0.54,2.20)	0.801	
Low	194	Low vs. Background	0.64 (0.22,1.85)	0.408	
High	185	High vs. Background	0.50 (0.15,1.67)	0.260	
Total	1,505				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant under both the minimal and maximal assumptions in the unadjusted analysis of tuberculosis (Table 17-7 [e] and [f]: p=0.614 and p=0.834, respectively).

In the adjusted analysis, the current dioxin-by-time interaction remained nonsignificant (Table 17-7 [g] and [h]: minimal, p=0.601; maximal, p=0.821).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast of the four current dioxin categories showed no significant association between tuberculosis and current dioxin in the unadjusted analysis (Table 17-7 [i]: p=0.486). No significant covariates were retained in the adjusted model therefore the results remained unchanged.

Physical Examination Variables

Thorax and Lung Abnormalities

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The association between thorax and lung abnormalities in Ranch Hands and initial dioxin was not significant under both the minimal and the maximal assumptions in the unadjusted model (Table 17-8 [a] and [b]: p=0.510 and p=0.131, respectively).

After the model was adjusted for covariates, the association between thorax and lung abnormalities and initial dioxin was marginally significant in the minimal analysis (Table 17-8 [c]: Adj. RR=1.27, p=0.088). The percentages of thorax and lung abnormalities were 5.4, 10.0, and 6.9 percent for the low, medium, and high levels of initial dioxin. Age and current cigarette smoking were the significant covariates that were retained in the adjusted model. In the maximal analysis, the risk of thorax and lung abnormalities became significant when lifetime cigarette smoking history and the interaction of age and current cigarette smoking were retained in the model (Table 17-8 [d]: Adj. RR=1.29, p=0.022). The percentages of thorax and lung abnormalities for the low, medium, and high initial dioxin levels were 4.3, 8.1, and 7.0 percent.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analysis of thorax and lung abnormalities, the interaction between current dioxin and time since tour was not significant under both assumptions (Table 17-8 [e] and [f]: p=0.496 for the minimal, p=0.829 for the maximal).

In the adjusted model, there was a significant interaction among current dioxin, time, and age for the minimal cohort (Table 17-8 [g]: p=0.012). To investigate this interaction age was divided into two categories: Ranch Hands who were born in or after 1942 and those born before 1942. The association between current dioxin and thorax and lung abnormalities was then examined within each age category for each time stratum. Within both age strata, the current dioxin-by-time interaction was not significant (Appendix Table P-1: born $\geq$1942: p=0.640; born <1942: p=0.150). However, for the younger Ranch Hands, the relative risk

TABLE 17-8.

Analysis of Thorax and Lung Abnormalities

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	5.4	1.09 (0.85,1.40)	0.510
	Medium	260	10.0		
	High	131	6.9		
b) Maximal (n=742)	Low	185	4.3	1.17 (0.96,1.42)	0.131
	Medium	371	8.1		
	High	186	7.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.27 (0.97,1.65)	0.088	AGE (p<0.001) CSMOK (p=0.002)
d) Maximal (n=742)	1.29 (1.04,1.60)	0.022	PACKYR (p=0.082) AGE*CSMOK (p=0.036)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-8. (Continued)

Analysis of Thorax and Lung Abnormalities

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.496[b]
(n=521)	≤18.6	1.4 (72)	10.2 (128)	1.9 (54)	1.18 (0.74,1.89)	0.477[c]
	>18.6	13.8 (58)	8.3 (132)	10.4 (77)	0.97 (0.71,1.34)	0.862[c]
f) Maximal						0.829[b]
(n=742)	≤18.6	5.7 (106)	4.7 (191)	7.2 (83)	1.11 (0.79,1.56)	0.552[c]
	>18.6	3.8 (79)	10.1 (179)	8.7 (104)	1.16 (0.91,1.49)	0.231[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.396**[b]	CURR*TIME*AGE (p=0.012)
(n=521)	≤18.6	1.51 (0.92,2.47)**	0.100**[c]	CSMOK (p=0.078)
	>18.6	1.18 (0.85,1.64)**	0.335**[c]	PACKYR (p=0.113)
h) Maximal			0.794[b]	PACKYR (p=0.087)
(n=742)	≤18.6	1.27 (0.87,1.84)	0.216[c]	AGE*CSMOK (p=0.037)
	>18.6	1.34 (1.03,1.76)	0.030[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-8. (Continued)

Analysis of Thorax and Lung Abnormalities

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	5.5	All Categories		0.301
Unknown	345	5.8	Unknown vs. Background	1.06 (0.62,1.84)	0.826
Low	196	8.7	Low vs. Background	1.64 (0.91,2.94)	0.097
High	187	8.0	High vs. Background	1.51 (0.82,2.78)	0.188
Total	1,514				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	786	All Categories		0.096	AGE (p<0.001) CSMOK (p<0.001)
Unknown	345	Unknown vs. Background	0.92 (0.52,1.62)	0.771	PACKYR (p=0.038)
Low	196	Low vs. Background	1.60 (0.87,2.94)	0.130	
High	187	High vs. Background	1.98 (1.04,3.78)	0.037	
Total	I,514				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

was less than 1 when time did not exceed 18.6 years and was greater than 1 when time exceeded 18.6 years. Conversely, for the older Ranch Hands, the relative risk when time was less than 18.6 years was greater than when time exceeded 18.6 years. For those Ranch Hands who were born before 1942 and whose time since tour was less than or equal to 18.6 years, the risk of thorax and lung abnormalities was significant (Adj. RR=1.89, p=0.038). The percentages of thorax and lung abnormalities within this stratum were 2.1, 16.1, and 7.7 percent for the low, medium, and high levels of current dioxin.

When the interaction was removed from the model, the current dioxin-by-time interaction was not significant (Table 17-8 [g]: p=0.396). But, when time since tour was restricted to being less than or equal to 18.6 years, the risk of thorax and lung abnormalities was marginally significant (Table 17-8 [g]: Adj. RR=1.51, p=0.100). The percentages of abnormalities within this stratum were 1.4, 10.2, and 1.9 percent for the low, medium, and high levels of current dioxin. After the current dioxin-by-time-by-age interaction was removed, age, current cigarette smoking, and lifetime cigarette smoking history were the covariates retained in the model.

Under the maximal assumption the current dioxin-by-time interaction in the adjusted model was also nonsignificant (Table 17-8 [h]: p=0.794). Within the stratum containing Ranch Hands whose time since tour was greater than 18.6 years, the risk of thorax and lung abnormalities became significant (Adj. RR=1.34, p=0.030). In the low, medium, and high current dioxin categories, 3.8, 10.1, and 8.7 percent of the Ranch Hands had thorax and lung abnormalities. The significant covariates that were retained in this model were lifetime cigarette smoking history and the age-by-current cigarette smoking interaction.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted analysis there was no significant overall association between the categorized current dioxin and thorax and lung abnormalities (Table 17-8 [i]: p=0.301). There was, however, a marginally significant risk of thorax and lung abnormalities when contrasting the low current dioxin category with the background current dioxin category (Est. RR=1.64, 95% C.I.: [0.91,2.94], p=0.097). The percentages of abnormalities for the background, unknown, low, and high categories were 5.5, 5.8, 8.7, and 8.0 percent.

After adjusting for age, current cigarette smoking, and lifetime cigarette smoking history, the overall association between categorized current dioxin and thorax and lung abnormalities became marginally significant (Table 17-8 [j]: p=0.096). The risk of thorax and lung abnormalities increased as the Ranch Hands' current dioxin levels increased. The adjusted relative risks were 0.92 for the unknown versus the background category contrast, 1.60 for the low versus the background category contrast, and 1.98 for the high versus the background category contrast. However, the only risk that was significant was the high versus background contrast (p=0.037, 95% C.I.: [1.04,3.78]). The risk for the low versus background contrast became nonsignificant after the model had been adjusted for the covariates (p=0.130).

Hyperresonance

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted model, the association between hyperresonance and initial dioxin was not significant for both the minimal and maximal analyses (Table 17-9 [a] and [b]: p=0.808 and p=0.359).

After the model was adjusted for significant covariates, the minimal analysis remained nonsignificant (Table 17-9 [c]: p=0.186). In the maximal analysis, however, there was a marginally significant risk of hyperresonance after the inclusion of age and current cigarette smoking in the model (Table 17-9 [d]: Adj. RR=1.30, p=0.076). The percentages of Ranch Hands in the maximal cohort with hyperresonance in the low, medium, and high initial dioxin categories were 2.2, 4.3, and 3.8 percent.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant in the unadjusted analysis of hyperresonance, under both the minimal and the maximal assumptions (Table 17-9 [e] and [f]: p=0.905 and p=0.567).

After the model was adjusted for significant covariates, the current dioxin-by-time interaction remained nonsignificant (Table 17-9 [g] and [h]: p=0.902 for the minimal cohort and p=0.574 for the maximal cohort). However, under the maximal assumption, after the model was adjusted for age and current cigarette smoking, the risk of hyperresonance became significant for the Ranch Hands whose time since tour was greater than 18.6 years (Table 17-9 [h]: Adj. RR=1.53, p=0.027). The low, medium, and high current dioxin categories had 0.0, 4.5, and 3.9 percent occurrences within this stratum. The association between hyperresonance and current dioxin remained nonsignificant for those with time less than or equal to 18.6 years (p=0.270).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The association between hyperresonance and the four current dioxin categories was not significant in the unadjusted model (Table 17-9 [i]: p=0.874).

After the model was adjusted for age and current cigarette smoking, the association between hyperresonance and the four current dioxin categories remained nonsignificant (Table 17-9 [j]: p=0.378). However, the contrast between the percentage in the high current dioxin category (4.3%) and the percentage in the background current dioxin category (3.1%) became marginally significant (p=0.086). The adjusted relative risk of hyperresonance was equal to 2.11 (95% C.I.: [0.90,4.97]) for this contrast.

Dullness

The following analyses included only three participants, two Ranch Hands and one Comparison, who had been diagnosed with dullness of the lungs. Such a small number of abnormalities limits the ability of these analyses to detect an association.

TABLE 17-9.

Analysis of Hyperresonance

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	4.6	1.04 (0.74,1.48)	0.808
	Medium	260	5.0		
	High	131	2.3		
b) Maximal (n=742)	Low	185	2.2	1.13 (0.87,1.48)	0.359
	Medium	371	4.3		
	High	186	3.8		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.29 (0.89,1.86)	0.186	AGE (p<0.001) CSMOK (p<0.001)
d) Maximal (n=742)	1.30 (0.98,1.73)	0.076	AGE (p<0.001) CSMOK (p<0.001)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-9. (Continued)

Analysis of Hyperresonance

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.905[b]
(n=521)	≤18.6	4.2 (72)	5.5 (128)	1.9 (54)	1.02 (0.58,1.79)	0.959[c]
	>18.6	6.9 (58)	3.8 (132)	2.6 (77)	1.06 (0.67,1.69)	0.802[c]
f) Maximal						0.567[b]
(n=742)	≤18.6	3.8 (106)	3.7 (191)	4.8 (83)	1.07 (0.71,1.60)	0.751[c]
	>18.6	0.0 (79)	4.5 (179)	3.9 (104)	1.25 (0.87,1.81)	0.228[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.902[b]	AGE (p<0.001)
(n=521)	≤18.6	1.46 (0.79,2.70)	0.231[c]	CSMOK (p<0.001)
	>18.6	1.39 (0.86,2.25)	0.179[c]	
h) Maximal			0.574[b]	AGE (p<0.001)
(n=742)	≤18.6	1.29 (0.82,2.05)	0.270[c]	CSMOK (p<0.001)
	>18.6	1.53 (1.05,2.23)	0.027[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-9. (Continued)

Analysis of Hyperresonance

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	3.1	All Categories		0.874
Unknown	345	3.2	Unknown vs. Background	1.05 (0.51,2.16)	0.904
Low	196	3.1	Low vs. Background	1.00 (0.40,2.49)	0.995
High	187	4.3	High vs. Background	1.42 (0.63,3.21)	0.401
Total	1,514				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	786	All Categories		0.378	AGE ($p<0.001$) CSMOK ($p<0.001$)
Unknown	345	Unknown vs. Background	0.92 (0.44,1.95)	0.834	
Low	196	Low vs. Background	0.98 (0.39,2.48)	0.971	
High	187	High vs. Background	2.11 (0.90,4.97)	0.086	
Total	1,514				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The minimal analysis of the unadjusted model exhibited no significant association between dullness and initial dioxin (Table 17-10 [a]: p=0.196). However, there was a marginally significant positive association in the maximal analysis (Table 17-10 [b]: Est. RR=2.07, p=0.094). The percentage of dullness occurrences became larger with the increase of the initial dioxin levels (0.0, 0.3, and 0.5 percent for the low, medium, and high levels).

After the model was adjusted for significant covariates, the association between dullness and initial dioxin remained nonsignificant in the minimal analysis (Table 17-10 [c]: p=0.158). In the maximal analysis the association remained marginally significant (Table 17-10 [d]: Adj. RR=2.52, p=0.051).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Since only two Ranch Hands were diagnosed with dullness, one in each of the time since tour strata, the results of the current dioxin and time analysis were inconclusive. The data for these two participants were 211 ppt current dioxin, and 16.8 years since tour for one individual, and 25.6 ppt current dioxin and 18.9 years since tour for the other.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

There were only two Ranch Hands and one Comparison in this analysis who were diagnosed with dullness of the lungs. The data for the two Ranch Hands are detailed above. The first belonged to the high current dioxin category, and the second belonged to the low category. The Comparison, who belonged to the background current dioxin category, had a current dioxin level of 5.9 ppt. The sparseness of occurrences made this analysis impractical.

Wheezes

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The association between initial dioxin and the occurrence of wheezes was not significant in the unadjusted model under either assumption (Table 17-11 [a] and [b]: p=0.132 for the minimal cohort and p=0.112 for the maximal cohort).

When the model was adjusted for covariates, the association between wheezes and initial dioxin became significant under both assumptions. For the minimal cohort, the adjusted relative risk was 1.53 after the inclusion of age and lifetime cigarette smoking history in the model (Table 17-11 [c]: p=0.034). The percentages of occurrences were 1.5, 3.1, and 4.6 percent for the low, medium, and high initial dioxin levels. For the maximal cohort, the adjusted relative risk was 1.42 when age, lifetime cigarette smoking history, and current cigarette smoking were included in the model (Table 17-11 [d]: p=0.034). The percentages of occurrences in this cohort were 2.2, 2.2, and 4.3 percent.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

For the unadjusted analysis of occurrence of wheezes, the current dioxin-by-time since tour interaction was not significant under both assumptions (Table 17-11 [e] and [f]: p=0.500 for the minimal and p=0.862 for the maximal). Therefore, under each assumption, the risk of wheezes did not differ significantly between time strata.

TABLE 17-10.

Analysis of Dullness

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.89 (0.76,4.75)	0.196
	Medium	260	0.4		
	High	131	0.8		
b) Maximal (n=742)	Low	185	0.0	2.07 (0.90,4.74)	0.094
	Medium	371	0.3		
	High	186	0.5		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.93 (0.82,4.57)	0.158	CSMOK (p=0.022)
d) Maximal (n=742)	2.52 (0.99,6.42)	0.051	PACKYR (p=0.032)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-10. (Continued)

Analysis of Dullness

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	1.9 (54)	--	--
	>18.6	0.0 (58)	0.8 (132)	0.0 (77)	--	--
f) Maximal						--
(n=742)	≤18.6	0.0 (106)	0.0 (191)	1.2 (83)	--	--
	>18.6	0.0 (79)	0.6 (179)	0.0 (104)	--	--

[a]Relative risk for a twofold increase in dioxin.
--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-10. (Continued)

Analysis of Dullness

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	0.1	All Categories		--
Unknown	345	0.0	Unknown vs. Background	--	--
Low	196	0.5	Low vs. Background	--	--
High	187	0.5	High vs. Background	--	--
Total	1,514				

--: Relative risk/confidence interval/p-value not given due to the sparse number of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 17-11.

Analysis of Wheezes

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	1.5	1.34 (0.93,1.93)	0.132
	Medium	260	3.1		
	High	131	4.6		
b) Maximal (n=742)	Low	185	2.2	1.28 (0.95,1.71)	0.112
	Medium	371	2.2		
	High	186	4.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.53 (1.05,2.23)	0.034	AGE (p=0.139) PACKYR (p=0.020)
d) Maximal (n=742)	1.42 (1.04,1.94)	0.034	AGE (p=0.043) CSMOK (p=0.042) PACKYR (p=0.114)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 17-11. (Continued)

Analysis of Wheezes

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.500[b]
(n=521)	≤18.6	0.0 (72)	3.1 (128)	1.9 (54)	1.57 (0.75,3.27)	0.229[c]
	>18.6	5.2 (58)	2.3 (132)	6.5 (77)	1.17 (0.75,1.82)	0.502[c]
f) Maximal						0.862[b]
(n=742)	≤18.6	1.9 (106)	1.6 (191)	2.4 (83)	1.28 (0.74,2.23)	0.375[c]
	>18.6	2.5 (79)	3.4 (179)	4.8 (104)	1.21 (0.85,1.73)	0.293[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.409**[b]	CURR*TIME*AGE (p=0.018)
(n=521)	≤18.6	1.95 (0.93,4.12)**	0.079**[c]	PACKYR (p=0.015)
	>18.6	1.36 (0.87,2.14)**	0.179**[c]	
h) Maximal			0.907[b]	AGE (p=0.045)
(n=742)	≤18.6	1.46 (0.81,2.63)	0.203[c]	CSMOK (p=0.042)
	>18.6	1.41 (0.97,2.04)	0.074[c]	PACKYR (p=0.127)

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 17-11. (Continued)

Analysis of Wheezes

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	786	1.9	All Categories		0.310
Unknown	345	3.5	Unknown vs. Background	1.85 (0.86,4.00)	0.117
Low	196	3.1	Low vs. Background	1.62 (0.62,4.24)	0.323
High	187	3.7	High vs. Background	2.00 (0.80,4.97)	0.137
Total	1,514				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	786	All Categories		0.399	AGE (p=0.039)
					RACE (p=0.114)
Unknown	345	Unknown vs. Background	1.47 (0.66,3.28)	0.350	CSMOK (p<0.001)
Low	196	Low vs. Background	1.52 (0.57,4.06)	0.408	PACKYR (p=0.056)
High	187	High vs. Background	2.28 (0.88,5.92)	0.092	
Total	1,514				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

When adjusted for significant covariates, there was a significant interaction among current dioxin, time since tour, and age in the minimal analysis (Table 17-11 [g]: p=0.018). To explore this interaction, age was divided into two strata. For those Ranch Hands who were born in or after 1942, the current dioxin-by-time interaction was not significant (Appendix Table P-1: p=0.417). For those born before 1942, the current dioxin-by-time interaction was marginally significant (p=0.067). Within this age stratum, the risk of the occurrence of wheezes was significantly greater than 1 when time was less than or equal to 18.6 years (Adj. RR=2.69, p=0.026). The percentage of occurrences of wheezes increased over the current dioxin levels from 0.0 percent for the low level to 4.8 percent for the medium level, and 7.7 percent for the high level. When time was greater than 18.6 years the risk was less than 1, but nonsignificant (Adj. RR=0.98, p=0.949). In contrast, for Ranch Hands born since 1942, the relative risk was less than 1 when time was less than or equal to 18.6 years (Adj. RR=0.75, p=0.775), and was greater than 1 when time was greater than 18.6 years (Adj. RR=1.70, p=0.188).

After this interaction was removed from the model, the current dioxin-by-time since tour interaction remained nonsignificant (Table 17-11 [g]: p=0.409). However, after the model had been adjusted for age and lifetime cigarette smoking history, the risk of wheezes became marginally significant when time was restricted to less than or equal to 18.6 years (Table 17-11 [g]: Adj. RR=1.95, p=0.079). When time was greater than 18.6 years, the association between wheezes and current dioxin remained nonsignificant (p=0.179).

Under the maximal assumption, the current dioxin-by-time since tour interaction also remained nonsignificant after the adjustment was made for covariates (Table 17-11 [h]: p=0.907). However, after age, current cigarette smoking, and lifetime cigarette smoking history were included in the model, the risk of the occurrence of wheezes became marginally significant for those Ranch Hands whose time since tour exceeded 18.6 years (Table 17-11 [h]: Adj. RR=1.41, p=0.074).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

In the unadjusted model there was no significant association between the four current dioxin categories and the occurrence of wheezes (Table 17-11 [i]: p=0.310).

After the model had been adjusted for covariates, the association between the current dioxin categories and wheezes remained nonsignificant (Table 17-11 [j]: p=0.399). However, for the contrast between the high current dioxin category and the background category, the risk of wheezes became marginally significant after including age, race, current cigarette smoking, and lifetime cigarette smoking history in the model (Table 17-11 [j]: Adj. RR=2.28, 95% C.I.: [0.88,5.92], p=0.092). The percentage of Comparisons in the background category with wheezes was 1.9 percent. The percentages of Ranch Hands with wheezes in the unknown, low, and high categories were 3.5, 3.1, and 3.7 percent.

Rales

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analysis, no significant association was found between initial dioxin and the occurrence of rales in Ranch Hands under either assumption (Table 17-12 [a] and [b]:

TABLE 17-12.

Analysis of Rales

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.23 (0.73,2.09)	0.448
	Medium	260	1.9		
	High	131	2.3		
b) Maximal (n=742)	Low	185	1.1	1.19 (0.78,1.81)	0.429
	Medium	371	1.4		
	High	186	1.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.52 (0.90,2.57)	0.142	AGE (p<0.001)
d) Maximal (n=742)	1.38 (0.89,2.14)	0.171	AGE (p<0.001)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.